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(57) Abstract: The invention relates to water soluble or water dispersible powders or tablets based on a carbohydrate matrix with improved dissolution properties in water. The powders or tablets or a precursor therefor are subjected to treatment with a gas so that gas is entrapped in the powder or tablet, which comprises providing the powder or tablet with sufficient closed porosity so that gas entrapped therein promotes dissolution or dispersion on contact with water. The powders or tablets may be pharmaceuticals or foods.

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WATER SOLUBLE POWDERS AND TABLETS

Field of the invention

This invention relates to water soluble or water dispersible carbohydrate based
5 powders and tablets with improved reconstitution properties in water.

Background to the invention

Water soluble powders and tablets based on amorphous carbohydrate matrices
are used in many fields. For example such powders or tablets in a form suitable for
10 human consumption are used in the food, beverage, nutrition, confectionery and
pharmaceutical fields. Alternatively the powders or tablets may contain materials
such as detergents intended to be dissolved or dispersed in water before use. In many
cases, it is desirable that the powders or tablets should dissolve or disperse rapidly on
contact with water and, for example, poor tablet dissolution is known to account for
15 many drug-bioavailability problems. The powder or tablet may contain a chemical
dissolution aid and such aids are generally combinations of chemicals which are
stable in solid form but which generate a gas on contact with water, for example the
combination of an acid and a carbonate or bicarbonate. In some cases the amount of
the gas-generating chemicals added is such as to provide effervescent powders or
20 tablets.

One particular type of water soluble carbohydrate powder is soluble foamer
and creamer powders which upon addition of a liquid are able to provide a creamy
foam and such powders have many uses. For example, they may be used to provide
milk shakes or cappuccino style beverages or they may have food applications such as
25 in desserts, soups and sauces. Soluble coffee beverage products which produce
cappuccino-type beverages are particularly well known and these are usually a dry
mix of a soluble coffee powder and a soluble beverage creamer. Products of this type
are known which contain pockets of gas which upon dissolution of the powder
produce a foam so that on the addition of water or milk (which will usually be hot) a
30 whitened coffee beverage is produced having foam on the surface which resembles, to
some extent at least, traditional Italian cappuccino. Examples of gassed soluble
beverage creamers are described in EP-A-0 154 192, EP-A-0 450 310 and EP-A-0

885 566. Soluble beverage creamers which contain chemical foaming agents are also known. The formation of a foam is dependent on the powder containing an ingredient, generally a protein such as casein, which is capable of stabilising a foam.

In many fields, the presence of gas-generating chemicals is undesirable, for example because of their effect on flavour, or may even be prohibited. There is a need to provide water soluble or water dispersible carbohydrate based powders and tablets with improved reconstitution properties in water without the need to use chemical dissolution aids.

10 Summary of the invention

According to one aspect, the present invention provides a method of increasing the solubility or dispersibility of a powder or tablet based on a carbohydrate matrix by subjecting the powder or tablet or a precursor therefor to treatment with a gas so that gas is entrapped in the powder or tablet, which comprises providing the powder or tablet with sufficient closed porosity so that gas entrapped therein promotes dissolution or dispersion on contact with water.

According to a further aspect, the present invention provides a non-foaming water soluble or water dispersible powder based on a carbohydrate matrix, said powder containing entrapped gas in an amount which is such as to promote dissolution or dispersion of the powder in contact with water.

According to a still further aspect, the present invention provides a water soluble or water dispersible tablet based on a carbohydrate matrix containing entrapped gas and having sufficient closed porosity to allow retention of entrapped gas in an amount which promotes dissolution or dispersion of the tablet on contact with water.

Detailed description of the invention

The powders and tablets with which the present invention is concerned may be based on any suitable carbohydrate or mixture of carbohydrates. Generally, the powder or tablet includes an amorphous carbohydrate matrix which will also include other components depending on the intended use of the powder or tablet. Tablets may consist of the carbohydrate matrix or more usually will comprise the carbohydrate

matrix together with one or more other ingredients. Examples of suitable carbohydrates include sugars such as lactose, dextrose, fructose, sucrose, maltodextrin, cyclodextrins and corn syrup, starch and modified starch. If the tablets or powders are not food grade, then any other kind of water soluble or water dispersible starch can be used. The carbohydrate generally makes up at least 50% by weight of the matrix, preferably at least 75% by weight of the matrix and more preferably at least 90% by weight of the matrix.

The properties of the matrix can be influenced and, in particular optimised, by addition of plasticisers, anti-plasticisers, fillers, compounds which influence the formation of crystallites or ordered regions in the material, cross-linking agents, emulsifiers, foam stabilisers, colorants and binders. Such additives preferably constitute no more than 25% by weight and more preferably no more than 10% by weight of the matrix. Tablets and powders may contain materials such as protein, hydrocolloids and fats. Tablets in particular may contain one or more active ingredients the nature of which will depend on the intended use of the tablets. Preferably the tablets and powders contain no more than 7% by weight water, more preferably no more than 5% by weight water and most preferably no more than 3% by weight water.

Where the powder or tablet is non-foaming, the composition should either contain insufficient amounts of foam stabilising components such as proteins to allow formation of a foam (or such components should be absent altogether), or it should contain a foam-destabilising agent. Examples of foam destabilising agents include isopropanol, fats and lipids, sucrose, monoesters, mono/diester mixtures and propylene glycol monostearate. In this connection the powder or tablet should preferably be non-foaming (minimal foam formation).

The powders and tablets according to the present invention include a gas entrapped therein. This may be any suitable gas which does not adversely affect the other components of the powder or tablets. Where the powder or tablets are intended for human consumption as a food, beverage, nutritional or pharmaceutical, the gas should be of food grade. Examples of suitable gases include nitrogen, carbon dioxide, air, oxygen, helium, hydrogen, argon, neon, methane, ethane, krypton, chlorine, chlorofluorocarbons and mixtures thereof. The amount of gas introduced into the

powder or tablet is preferably at least 3ml(STP)/g, more preferably at least 5ml(STP)/g and most preferably at least 7ml(STP)/g.

The gas may be introduced into the powder or tablet or a precursor thereof by any suitable process. One suitable technique for forming powders involves providing a matrix in the form of expanded particles and then entrapping gas in the particles. In general the method involves heating the powder under pressure of the gas at a temperature at which the matrix softens, which may be a temperature above the glass transition point (T_g) of the matrix. Gas enters into the particles which become loaded with the gas and the particles are solidified by quenching to retain the gas in the particles. The particles containing the gas may be the final form of the product or they be admixed with a further powder form component to form the final powder product.

The expanded particles may be produced by injecting a gas into an aqueous matrix concentrate having a solids content suitable for spray drying, generally above about 30% by weight. The gas may be injected into the aqueous matrix concentrate at a pressure of about 500 kPa to about 5 MPa although the pressure at which the gas is injected is generally not critical. The gassed aqueous matrix is then spray dried to a powder. The particles are then subjected to an inert gas atmosphere at high pressure and at a temperature above softening point of the matrix, which for an amorphous carbohydrate matrix may be the same as or similar to the T_g of the matrix. The pressure may be from about 100 kPa gauge to about 20 MPa gauge. The temperature required will depend on the composition of the particles since this will influence the T_g but can readily be determined for any particle type and composition. The use of temperatures more than about 50°C above the T_g of the particles is unnecessary and best avoided. The particles may be subjected to the pressure and temperature for as long as desired since increasing the time will generally increase gas entrapment but times from about 10 seconds to about 30 minutes are generally sufficient. The particles are then subjected to rapid quenching or curing to ensure entrapment of the gas. Suitable cooling procedures may be used to quench the particles.

Another suitable technique for introducing gas into particles involves injecting gas into a molten mass of the matrix for the particles which contains little or no moisture, for example in an extruder. The gas may be injected at a pressure of about 100 kPa gauge to about 20 MPa gauge. The temperature required will depend on the

composition of the matrix since this will influence the melt temperature but can readily be determined for any matrix type and composition. Temperatures above about 150°C should generally be avoided. The molten mass may then be extruded through a small orifice and comminuted into a powder. Depending on the rapidity of solidification of the matrix, the matrix may need to be cured or quenched under pressure before being formed into a powder to prevent the gas escaping from the matrix. Curing or quenching is preferably carried out rapidly and the time may vary for example from about 10 seconds to about 90 minutes.

If the final product is a powder it may be used in the form in which it is produced by the above method or it may be mixed with other ingredients in powder form. In this case the gas containing powder may act as a dissolution aid for the overall powder. Any active ingredients are preferably incorporated into the powder before gas loading.

Where the final product is a tablet, this may be produced in a conventional manner and subsequently loaded with gas. The process by which a particulate solid may be transformed into a tablet by the application of pressure can be divided into the two stages of consolidation and bond formation and the ability of a powder to form a tablet is dependent on a balance between the plastic deformation and the brittle fracture properties of the powder particles. Tablets may be formed by direct compression of powders and in some cases lubricants such as magnesium stearate are used to improve powder compaction. In addition, binding agents are usually applied. Within the embodiments of the present invention, these binders are for example, but not exclusively, carbohydrates, starches in native or treated form, lipids, waxes and fats. Many parameters influence powder compaction including the composition, particle size, water content, compaction speed and pressure, the way in which the powder was prepared (roller dried, spray dried, freeze dried), powder flowability and powder brittleness. Further information on tablet formation can be found in standard reference works such as Pharmaceutical Powder Compaction Technology (1996) Ed. Alderborn, G and Nyström, C, Marcel Dekker, New York.

According to one embodiment, foamed powders, for example foamed food powders, prepared by extruding, spray-drying or freeze-drying, and which have a high level of closed porosity, are compacted into tablets as described above and then

loaded with gas by the same general method as described above for the production of powders. The holding time, for example pressurization time above T_g , plays an important role and the loading time and volume of gas entrapped depends on loading conditions and matrix composition.

5 It may also be possible to form pressurized powders with high closed porosity and containing a high volume of entrapped gas directly into tablets, optionally together with other ingredients. Compaction of the tablet premix must be carried out in such a way that a significant proportion of the closed porosity remains. By use of relatively low compaction pressures, most of the gas is retained in the tablet (closed
10 pores) and it is also possible to optimise to open porosity thereby improving dissolution properties of the tablet. If the powder is softened, for example by increasing the temperature, the particles can be compacted without significant cracking thereby minimising gas loss during compaction. Where gas containing powder is compacted with other powder form ingredients to form tablets, the gas
15 containing component can act as a dissolution aid for the tablet as a whole.

Where carbohydrate-based tablets or powders include a gas-containing component as a dissolution aid, this component may make up 0.5 to 70% by weight of the total composition. In the final formulation, the gas-containing component generally has a softening point and/or T_g of at least 35°C , more preferably at least
20 45°C , and most preferably at least 55°C . In the case where the matrix is based on an amorphous carbohydrate, the softening point may be but is not exclusively restricted to T_g .

The production of particles and tablets loaded with gas requires the gas to be transported into and entrapped by the matrix forming the particles and tablets and it
25 has been found that the mechanism of gas transport and entrapment is related to the matrix composition and, in particular, to the closed porosity of the matrix. Gas enters the matrix at temperatures above the T_g as a result of lowered matrix viscosity and increased matrix mobility. The optimum temperature range for gas to enter the matrix depends on the composition of the matrix but can readily be determined in any
30 particular case. Below the T_g of the matrix the rate of gas entrapment is very low and if the temperature increases too far above the T_g the matrix tends to collapse reducing gas entrapment. Within the optimum temperature range, the amount of gas entrapped

increases with increased loading pressure and with increased holding time until equilibrium is reached between the pressure inside and outside the matrix.

Closed pores in the matrix are able to hold gas under pressure for prolonged periods of time and, provided that there are no cracks in the matrix, release is confined by diffusion through the glassy matrix. Good gas retention thus requires an adequate closed pore volume after loading with gas and the matrix should be resistant to cracking of the surrounding lamellae.

Non-foaming carbohydrate powders or tablets will generally contain no protein or only a small amount of protein, although if necessary a small amount of foam stabiliser can be added to obtain a powder with initial closed pores. Suitable foam stabilisers are generally proteins such as casein or whey and they may be added in an amount of, for example, up to 5% or 10%, but the exact level is not critical. The powder may contain any desired non-foaming ingredients such as fats and salts and active ingredients are included as appropriate depending on the intended use of the composition. Surface active ingredients besides whey proteins or sodium caseinate may be used to create initial closed pores in the powder and examples of such ingredients include saponin, surface active lipids and other proteins such as lysozyme. Porosity may also be formed by rapid quenching of gassed powders or tablets, rapid release of elevated external pressure in the softened state, or by using blowing agents, for example isobutane or halogenated chlorofluorocarbons, at elevated pressures and/or temperatures.

In one embodiment of the invention, the tablets or powder comprise a beverage base, e.g coffee, cocoa, malt or tea. In particular tablets comprising soluble coffee have been found to be readily disolvable and dispersable. For example, the tablets may comprise soluble coffee, foamed powder, sugar and creamer.

Upon reconstitution of the powder or tablet, the particles containing entrapped gas will crack, break up or disintegrate, thereby increasing the specific surface area of the powder or the tablet which promotes the dispersion and subsequent dissolution of the powder or the tablet.

An additional advantage of the present invention is that, if an inert gas is entrapped in the particles, its incorporation will protect any sensitive active ingredients present in the powder or tablet from interaction with atmospheric gases by

saturation of the powder or tablet with the inert gas. During storage, the loss of inert gas from the direct environment of the sensitive active ingredient will be partially compensated by the very slow release of gas from the entrapment matrix. In practice, the sensitive active ingredient will often be susceptible to oxidation and a suitable inert gas for protection is then nitrogen, although other inert gases may also
5 beneficially be used.

Examples of carbohydrate based tablets and powders according to the present invention include the following:

tablets and powders for pharmaceutical use containing gas which provide
10 better dispersion of the drugs that they contain;

tablets and powders containing gas for food supplement applications which show better dispersion of such materials as enzymes, probiotic bacteria and vitamins;

tablets and powders containing gas for food application, for example instant food powders;

15 tablets containing gas in the form of bonbons, for example for the confectionery field, tablets and powders for infant nutrition and tablets for the culinary field such as bouillon cubes;

cleaning tablets or powders such as tablets containing agents to clean contact lenses;

20 tablets or chewing gums for cleaning teeth upon wetting/chewing in the mouth where dissolution speed may affect uptake of sodium fluoride in the mouth;

tablets or powders for animal consumption, for example pet foods containing gas, flavours and nutritional ingredients, for example vitamins or probiotic microorganisms and their metabolites;

25 tablets and powders containing agrochemical ingredients for example fertilizers, pesticides or herbicides;

tablets and powders containing cosmetic ingredients, for example bath and shower preparations.

It would be understood that this technology would also be applicable to other fields
30 such as household products.

The invention is illustrated by the following examples.

Example 1 - Preparation of tablets and powders

Tablets were prepared from freeze-dried amorphous powders (particle size between 0.4 and 0.9 mm) consisting of maltodextrin DE 12 (Sugro, AG Switzerland) with varying percentage of sodium caseinate (Säntis, AG, Switzerland) (Table 1).

5 The tablets (diameter 38 mm, height 2 mm) were compressed with an estimated tableting pressure of 260 MPa using a standard workshop presss (PRM 60 PHP, Rassant, France).

Table 1 Composition of samples used for tablet compression

Sample	Maltodextrin DE 12 (wt.%)	Sodium caseinate
(wt.%)		
1	90	10
2	80	20
3	70	30

Example 2 - Gas loading

The procedure for loading the samples with nitrogen gas is as follows. First, the samples are pressurized with nitrogen gas at room temperature in a closed batch autoclave (volume 5 liter, type DN 2000 (Meili S.A, Switzerland), maximum pressure 30 bar). The autoclave is equipped with a temperature sensor (PT-100, no. AC 1912, Rotronic, Switzerland), relative humidity sensor (HP101A-L5-ES1W, Rotronic, Switzerland), pressure sensor (ED 510/354.461/105, Haenni, Switzerland) and mixer (UFM1-F, SAIA). Second, the powder is heated under pressure to temperatures above its glass transition temperature. Above the T_g, the gas is readily taken up by the sample. The gas is retained in the sample by relieving the pressure in the vessel only after cooling the powder to temperatures below its glass transition temperature. The total amount of gas absorbed can be varied by varying the loading temperature, pressure and time above T_g.

Example 3 - Tablets

Powder sample 3 with A_w 0.32 (see Example 1 above) is light compressed (compaction pressure ~20 kPa) and loaded in an autoclave according to method

described above. The compaction pressure is much lower than the compaction pressure normally used for the production of tablets. By lowering the compaction pressure, tablets with higher closed and open porosity can be obtained. In this connection reference is made to Figure 1a and 1b which represent the tablet (Figure 1a) and the granule in the tablet (Figure 1b). In these figures the legend is as follows:

1= solid matrix: matrix excluding both open and closed pores

2= voids: space or interstice between particles

3= open pore: cavity or channel communicating with the surface of the solid

4= micropore: pore $< 20 \text{ \AA}$

5= closed pore: cavity not communicating with the surface

6= crack: volume of thin fractures inside the solid matrix

7= connected pore: pore in connection with another pore or void volume

The loading pressure was 50 bar, loading time 60 min. and loading temperature 90°C .

The density of the tablet for gas loading is 1.3532 g/cm^3 and after gas loading 1.3069

g/cm^3 . After gas loading a closed porosity of 13% is measured, an open porosity of 58% and the tablet contains 5.3 ml/g gas, showing improved dissolution.

Example 4 - Powder

Powder sample 2 with Aw 0.23 is pressurized in an autoclave according to method described above. Pressure 50 bar, holding time 1 hour, temperature 120°C . The powder contains after gassing a closed porosity of 52%, density 0.73 g/cm^3 and 25 ml gas/gram. Upon reconstitution this powder dissolves very fast.

Example 5- Beverage tablets

Tablets were compacted from the following two premixes:

Sample	Soluble coffee ¹ [wt. %]	Foamed powder ² [wt. %]	Sucrose ³ [wt. %]	Creamer ⁴ [wt. %]
1	67	-	33	-
2	15	25	-	60

1) Spray-dried soluble coffee powder.

2) Foamed carbohydrate powder (dairy based).

3) Crystalline sucrose.

4) Spray-dried creamer powder.

Tablets (diameter 2 cm, thickness about 7 mm, tablet weight about 4 g) were compacted at low to medium compaction pressure using a manual tablet press. Samples were loaded with nitrogen after compaction. The loading conditions were
5 90 bar and 95 °C. The loading time was 30 minutes. Afterwards, dissolution tests were carried out in water of about 70 °C. The gas-loaded tablets dissolved noticeably more rapidly than the ones which were not loaded with gas. The sample containing the creamer also formed some foam on top of the beverage.

CLAIMS:

1. A method of increasing the solubility or dispersibility of a powder or tablet based on a carbohydrate matrix by subjecting the powder or tablet or a precursor therefor to treatment with a gas so that gas is entrapped in the powder or tablet, which comprises providing the powder or tablet with sufficient closed porosity so that gas entrapped therein promotes dissolution or dispersion on contact with water.
2. A method according to claim 1 wherein the powder or tablet has an amorphous carbohydrate matrix.
3. A method according to claim 1 or 2 wherein the carbohydrate is a sugar, starch or modified starch.
4. A method according to any of claims 1 to 3 wherein the carbohydrate comprises at least 50% by weight of the matrix.
5. A method according to claim 4 wherein the carbohydrate comprises at least 75% by weight of the matrix.
6. A method according to claim 5 wherein the carbohydrate comprises at least 90% by weight of the matrix.
7. A method according to any of claims 1 to 6 wherein the powder or tablet also contains protein, hydrocolloid or fat.
8. A method according to any of claims 1 to 7 wherein the gas is nitrogen, carbon dioxide, air, oxygen, helium, hydrogen, argon, neon, methane, ethane, krypton, chlorine, a chlorofluorocarbon or a mixture thereof.
9. A method according to any of claims 1 to 8 wherein the powder or tablet contains at least 3ml(STP)/g of gas.
10. A method according to claim 9 wherein the powder or tablet contains at least 5ml(STP)/g of gas.
11. A method according to claim 10 wherein the powder or tablet contains at least 7ml(STP)/g of gas.
12. A method according to any of claims 1 to 11 wherein for the production of a powder, gas is entrapped in the carbohydrate in the form of expanded particles.

13. A method according to claim 12 wherein gas is introduced into the particles by subjecting the particles at a temperature above the softening point of the carbohydrate to an atmosphere of the gas under pressure.

14. A method according to any of claims 1 to 11 for the production of
5 tablets which comprises forming a tablet from particles including the carbohydrate and entrapping gas in the carbohydrate.

15. A method according to claim 14 wherein the gas is introduced into the tablets by subjecting the tablets at a temperature above the Tg of the carbohydrate to an atmosphere of the gas under pressure.

10 16. A method according to any of claims 1 to 15 wherein the powder or tablet is a pharmaceutical or a food.

17. A method according to any of claims 1 to 15 for increasing the solubility or dispersibility of a tablet which comprises a carbohydrate matrix and one or more active ingredients.

15 18. A non-foaming water soluble or water dispersible powder based on a carbohydrate matrix, said powder containing entrapped gas in an amount which is such as to promote dissolution or dispersion of the powder in contact with water.

19. A powder according to claim 18 which has an amorphous carbohydrate matrix.

20 20. A powder according to claim 18 or 19 wherein the carbohydrate is a sugar, starch or modified starch.

21. A powder according to any of claims 18 to 20 wherein the carbohydrate comprises at least 50% by weight of the matrix

22 A powder according to claim 21 wherein the carbohydrate comprises at
25 least 75% by weight of the matrix

23 A powder according to claim 22 wherein the carbohydrate comprises at least 90% by weight of the matrix.

24 A powder according to any of claims 18 to 23 which contains less than 5% by weight foaming protein.

30 25. A powder according to any of claims 18 to 24 which contains a foam-destabilising agent.

26. A powder according to any of claims 18 to 25 wherein the gas is nitrogen, carbon dioxide, air, oxygen, helium, hydrogen, argon, neon, methane, ethane, krypton, chlorine, a chlorofluorocarbon or a mixture thereof.

27. A powder according to any of claims 18 to 26 which contains at least 3ml(STP)/g of gas.

28. A powder according to claim 27 which contains at least 5ml(STP)/g of gas.

29. A powder according to claim 28 which contains at least 7ml(STP)/g of gas.

30. A powder according to any of claims 18 to 29 which is a pharmaceutical or a food.

31. A method for the production of a powder according to any of claims 18 to 30 wherein gas is entrapped in the carbohydrate in the form of expanded particles.

32. A method according to claim 31 wherein gas is introduced into the particles by subjecting the particles at a temperature above the softening point of the carbohydrate to an atmosphere of the gas under pressure.

33. A water soluble or water dispersible tablet based on a carbohydrate matrix containing entrapped gas and having sufficient closed porosity to allow retention of entrapped gas in an amount which promotes dissolution or dispersion of the tablet on contact with water.

34. A tablet according to claim 33 which has an amorphous carbohydrate matrix.

35. A tablet according to claim 33 or 34 wherein the carbohydrate is a sugar, starch or modified starch.

36. A tablet according to any of claims 33 to 35 wherein the carbohydrate comprises at least 50% by weight of the matrix.

37. A tablet according to claim 36 wherein the carbohydrate comprises at least 75% by weight of the matrix.

38. A tablet according to claim 37 wherein the carbohydrate comprises at least 90% by weight of the matrix.

39. A tablet according to any of claims 33 to 38 which also contains protein, hydrocolloid or fat.

40. A tablet according to any of claims 33 to 39 wherein the gas is nitrogen, carbon dioxide, air, oxygen, helium, hydrogen, argon, neon, methane, ethane, krypton, chlorine, a chlorofluorocarbon or a mixture thereof.

5 41. A tablet according to any of claims 33 to 40 which contains at least 3ml(STP)/g of gas.

42. A tablet according to claim 41 which contains at least 5ml(STP)/g of gas.

43. A tablet according to claim 42 which contains at least 7ml(STP)/g of gas.

10 44. A tablet according to any of claims 33 to 43 which is a pharmaceutical or a food.

45. A tablet according to any of claims 33 to 43 which comprises a carbohydrate matrix and at least one active ingredient.

15 46. A method for the production of a tablet according to any of claims 33 to 45 which comprises forming a tablet from particles including the carbohydrate and entrapping gas in the carbohydrate matrix.

47. A method according to claim 46 wherein the gas is introduced into the tablets by subjecting the tablets at a temperature above the softening point of the carbohydrate matrix to an atmosphere of the gas under pressure.

I/I

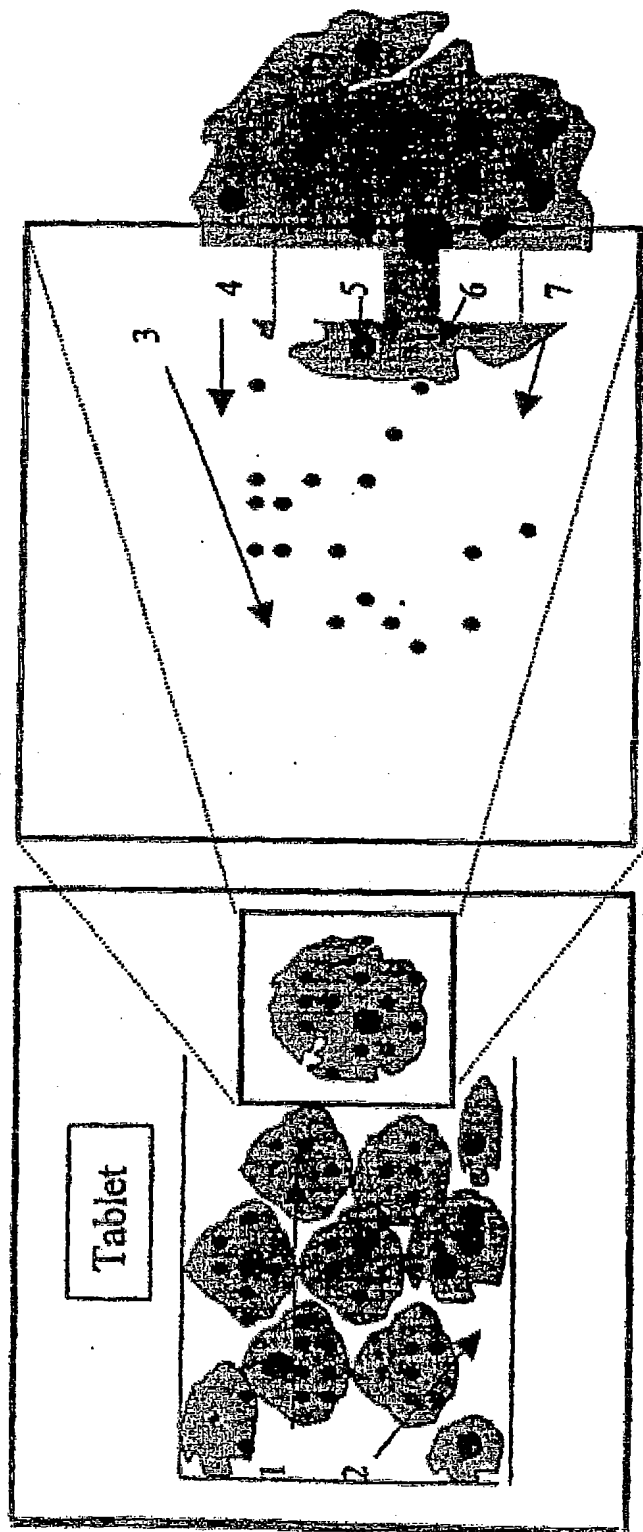


Fig. 1b

Fig. 1a

SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

national Application No

PCT/EP 02/00782

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A23C9/152 A23C11/00 A23K1/00 A23K1/18 A23P1/02
 A23L1/40 A23G3/30 A23G3/00 A23G3/02 C11D3/22
 C11D17/00 A61K7/00 A23F5/38 A61K9/20 A01N25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C11D A23C A23P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, FSTA, BIOSIS, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 382 437 A (ECANOW BERNARD) 17 January 1995 (1995-01-17)	1-12, 14, 16-23, 26-31, 33-46
A	page 1, line 46-63; example 1 column 4, line 67,68 ---	13,15, 24,25, 32,47
X	EP 0 450 141 A (NEOPHORE TECH INC) 9 October 1991 (1991-10-09) column 2, line 29-48; claims 1,4; example 1 column 11, line 33 -column 12, line 5 --- -/--	1-12, 14, 16-24, 26-31, 33-46

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

29 May 2002

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05/06/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Koch, J

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 298 261 A (PEBLEY WALTER S ET AL) 29 March 1994 (1994-03-29) abstract; claims 1,3,7	1-9, 12, 14-24, 26, 27, 30, 31, 33-41, 45, 46
X A	US 5 271 928 A (SCHNEIDER MICHEL ET AL) 21 December 1993 (1993-12-21) column 5, line 67 -column 6, line 32; examples 4,6,9 column 7, line 46 -column 8, line 61 column 9, line 67 -column 10, line 5	1-12, 17-31 13-15, 32-47
X A	WO 98 07329 A (NESTLE SA) 26 February 1998 (1998-02-26) page 3, line 10 -page 4, line 15 page 6, line 27 -page 7, line 7	1-9, 12, 16, 17, 31 13-15, 18-30, 32-47
X	US 4 746 527 A (KUYPERS THEO W) 24 May 1988 (1988-05-24) cited in the application column 2, paragraphs 3-5; claim 1 & EP 0 154 192 A 11 September 1985 (1985-09-11)	1-9, 12, 13, 16, 17, 31, 32
X	EP 0 579 328 A (CAMPINA MELKUNIE BV) 19 January 1994 (1994-01-19) claims 1,7	1-5, 7-9, 12, 16, 17, 31
X A	EP 0 885 566 A (NESTLE SA) 23 December 1998 (1998-12-23) cited in the application page 3, line 2-10; example 1	1-5, 7-9, 12, 16, 17, 31 13-15

INTERNATIONAL SEARCH REPORT

national Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5382437	A	17-01-1995	NONE
EP 0450141	A	09-10-1991	US 5039540 A 13-08-1991
		US 5079018 A 07-01-1992	
		CA 2023200 A1 15-02-1991	
		CY 1923 A 07-03-1997	
		DE 69019817 D1 06-07-1995	
		DE 69019817 T2 05-10-1995	
		DK 450141 T3 24-07-1995	
		EP 0450141 A1 09-10-1991	
		HK 118096 A 12-07-1996	
		JP 3086837 A 11-04-1991	
		NO 300085 B1 07-04-1997	
		NO 965460 A 15-02-1991	
US 5298261	A	29-03-1994	AU 5960294 A 19-07-1994
		WO 9414422 A1 07-07-1994	
US 5271928	A	21-12-1993	AT 125711 T 15-08-1995
		AU 630030 B2 15-10-1992	
		AU 7582891 A 30-10-1991	
		CA 2056371 A1 03-10-1991	
		CN 1055298 A , B 16-10-1991	
		DE 69111719 D1 07-09-1995	
		DE 69111719 T2 04-04-1996	
		DK 474833 T3 30-10-1995	
		WO 9115244 A2 17-10-1991	
		EP 0474833 A1 18-03-1992	
		ES 2075438 T3 01-10-1995	
		GR 3017324 T3 31-12-1995	
		IE 911048 A1 09-10-1991	
		IL 97730 A 08-12-1995	
		IN 172208 A1 01-05-1993	
		JP 11071265 A 16-03-1999	
		JP 2842453 B2 06-01-1999	
		JP 4506670 T 19-11-1992	
		KR 9602184 B1 13-02-1996	
		NZ 237637 A 25-06-1992	
		US 6136293 A 24-10-2000	
		US 5911972 A 15-06-1999	
		US 5380519 A 10-01-1995	
		US 5531980 A 02-07-1996	
		US 2001008626 A1 19-07-2001	
		US 2001012507 A1 09-08-2001	
		US 5658551 A 19-08-1997	
		US 5567414 A 22-10-1996	
		US 5643553 A 01-07-1997	
		US 2001024640 A1 27-09-2001	
		US 6110443 A 29-08-2000	
		ZA 9102427 A 29-01-1992	
WO 9807329	A	26-02-1998	US 6287616 B1 11-09-2001
		AU 733434 B2 17-05-2001	
		AU 3942497 A 06-03-1998	
		CN 1233152 A 27-10-1999	
		WO 9807329 A1 26-02-1998	
		EP 0923301 A1 23-06-1999	
		JP 2000516096 T 05-12-2000	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/00782

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4746527	A	24-05-1988	AT 36112 T 15-08-1988
			AU 576552 B2 01-09-1988
			AU 3845685 A 29-08-1985
			CA 1222410 A1 02-06-1987
			DE 3564071 D1 08-09-1988
			EP 0154192 A1 11-09-1985
			ES 540505 D0 01-12-1985
			ES 8602361 A1 16-03-1986
			GB 2154422 A ,B 11-09-1985
			GR 850401 A1 14-06-1985
			IE 55934 B1 27-02-1991
			IN 163753 A1 05-11-1988
			JP 1648641 C 13-03-1992
			JP 3013857 B 25-02-1991
			JP 60196148 A 04-10-1985
			KR 8903697 B1 30-09-1989
			MX 164783 B 23-09-1992
			NO 850654 A ,B, 21-08-1985
			NZ 211046 A 28-10-1988
			PH 21353 A 15-10-1987
			PT 79986 A ,B 01-03-1985
			SG 22888 G 30-09-1988
			US 4748040 A 31-05-1988
			ZA 8500873 A 25-09-1985
EP 0579328	A	19-01-1994	NL 9201264 A 01-02-1994
			AT 132704 T 15-01-1996
			CA 2100032 A1 15-01-1994
			DE 69301287 D1 22-02-1996
			DE 69301287 T2 18-07-1996
			DK 579328 T3 20-05-1996
			EP 0579328 A1 19-01-1994
			ES 2083820 T3 16-04-1996
			US 5462759 A 31-10-1995
EP 0885566	A	23-12-1998	EP 0885566 A1 23-12-1998
			AU 733541 B2 17-05-2001
			AU 7194098 A 24-12-1998
			BR 9802018 A 20-07-1999
			CA 2234043 A1 19-12-1998
			HU 9801381 A2 01-02-1999
			JP 11056233 A 02-03-1999
			NO 982682 A 21-12-1998
			NZ 330417 A 29-07-1999
			PL 326859 A1 21-12-1998
			TW 391862 B 01-06-2000
			ZA 9805330 A 20-12-1999